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Importance and comparison of inflammatory biomarkers in COVID-19 patients follow-up in intensive care unit

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ABSTRACT

Aims: This study aimed to determine the power of laboratory parameters and biomarkers in predicting the prognosis of patients admitted to the intensive care units (ICU) with COVID-19 in a state hospital.

Methods: In this retrospective study, the hospital automation system of all patients admitted to Bolu İzzet Baysal State Hospital's ICUs because of COVID-19 between March 2020 and December 2021 were recorded and examined. Demographic data, blood tests, APACHE II score, and inflammatory biomarkers were also recorded. The results of patients who survived and did not survive were compared.

Results: The study included 452 patients and the mortality was 72.6%. Exitus patients had higher APACHE II scores and age. The mortality rate was significantly higher in patients with neurological disorders. For patients who did not survive, blood leukocyte, procalcitonin, LDH, and creatinine levels were higher, whereas blood lymphocyte and thrombocyte levels were lower. Based on the ROC analyses, the lymphocyte count AUC was 0.624, APACHE II score AUC was 0.618, serum procalcitonin level AUC was 0.584, and platelet count was 0.560. Age, APACHE II score, neutrophil-to-lymphocyte ratio, and lymphocyte count were associated with mortality according to a univariate logistic regression analysis. Age (OR (95 CI%)1.02 (1.00-1.04, p=0.018)), APACHE II (OR (95 CI%)1.05 (1.01-1.09, p=0.018)), and neutrophil to lymphocyte ratio (OR (95 CI%) 1.02 (1.01-1.03, p=0.003)) were associated with mortality according to multivariate logistic regression

Conclusion: For patients admitted to the ICU, laboratory parameters and inflammatory biomarkers can help in diagnosis, follow-up, and prognosis in COVID-19. We believe that combinations of hemogram parameters are effective in predicting clinical follow-up and prognosis.

Keywords: Intensive care unit, mortality, COVID-19, lymphocyte, neutrophil-to-lymphocyte ratio

INTRODUCTION

In December 2019, pneumonia causing acute respiratory failure was observed for the first time in Wuhan, China, which was named COVID-19 in February 2020.[1] The disease can exhibit varying clinical spectrum, from asymptomatic infection to viral pneumonia, which can result in death.[2]

Oxygen therapy, mechanical ventilation support, renal replacement therapy, and other mechanical support systems are required in intensive care units (ICU) for patients with severe respiratory failure.[3] Care is provided to critically ill patients in the ICU, and understanding the factors that affect the outcomes of intensive care patients is useful, in terms of both the effective use of ICU beds and their cost.

This study aimed to investigate the clinical and laboratory parameters affecting the outcomes of patients admitted to the ICU owing to COVID-19. Our secondary aim was to compare the effects of inflammatory biomarkers, such as red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein-to-albumin ratio (CRP/Alb), and procalcitonin (PCT), on mortality.

METHODS

This retrospective study was conducted by examining the records in the hospital automation system of all patients admitted to Bolu İzzet Baysal State Hospital ICUs because of COVID-19 between March 2020 and December 2021. Patients >18 years of age with COVID-19 PCR results were included in this study. Patients with missing data, those <18 years of age and according to radiological imaging or blood tests, suspicious cases were excluded. Routine blood tests, comorbid conditions, age, sex, ICU length of stay (LoS), and Acute Physiology, Assessment, and Chronic Health Evaluation (APACHE) II values of patients included in the study were recorded when they were admitted to the ICU. The patients were divided into two groups, non-surviving and surviving, and the factors affecting mortality were compared. This study was approved by the Bolu Abant İzzet Baysal University

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Clinical Researches Ethics Committee (Date: 22.06.2021, Decision No: 2021/161). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis

For descriptive statistics, the mean±SD was used with a normal distribution. Categorical variables are expressed as numbers and percentages. Shapiro–Wilk, Kolmogorov–Smirnov, and Anderson-Darling tests were performed. The Mann–Whitney U test was used to compare age, APACHE II score, ICU LoS, and laboratory parameters in terms of mortality between the two independent groups. Pearson's X^2 and Fisher's exact tests were used to compare the differences between categorical variables (sex and comorbidities) in terms of mortality. Univariate and multivariate logistic regression analyses were performed to analyze the factors affecting mortality. Cut-off values were determined using the Youden and Delong method for receiver operating characteristic (ROC) analysis of leukocytes, lymphocytes, and platelets; PCT; RDW; NLR; CRP/Alb; creatinine; and lactate dehydrogenase (LDH), which predict mortality. The area under the curve (AUC) and corresponding 95% confidence interval (CI) were calculated using the MedCalc Statistical Software Trial Version (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2015). For statistical analysis, the Jamovi project (2020), Jamovi, and JASP (JASP, Amsterdam, Holland; Version 0.16.0.0), were used. Statistical significance was set at p-value of 0.05.

RESULTS

The study group included 452 patients with an average age of 71.3±13.6 years. Two hundred and forty-eight (54.9%) patients were men. Hypertension (HT) and neurological disorders were the two most common comorbidities, observed in 34.7% and 26.8% of the patients, respectively. The median APACHE II score was 21. The demographic and clinical characteristics of the patients are presented in Table 1.

The mortality rate in the study group was 72.6% (328 patients). We observed significant differences in age, APACHE II scores, and proportion of neurological disorders between surviving and non-surviving patients (p<0.05) (Table 1). The non-surviving patients were significantly older than the survivors (72.3±13.3 years vs. 68.7±14.0 years, p=0.010). The number of men and women were similar between the groups (p=0.999). The non-survivor group had a higher proportion of patients with neurological disorders (30.5% vs. 16.9%, p=0.005) than the survivor group. Non-surviving patients had significantly higher APACHE II scores than survivors (22.0 vs. 19.0, p<0.001). Other characteristics of the surviving and non-surviving patients are presented in Table 1.

Table 2 presents the laboratory results of the study groups. Laboratory parameters differed between the groups (p<0.05).

Table 2. Laboratory investigations of the survived and non-survived patients

	Patient groups		p*
	Survived (n=124)	Non-survived (n=328)	
Leukocyte count ($\times10^9$/L)‡	10.6 [2.6-43.9]	12.7 [1.9-66.8]	0.019
Lymphocyte count ($\times10^9$/L)‡	0.5 [0.0-3.1]	0.4 [0.0-4.2]	<0.001
Platelet count ($\times10^9$/L)‡	224.0 [22.0-707.0]	208.0 [17.5-649.0]	0.047
Procalcitonin& (ng/ml)‡	0.3 [0.0-33.5]	0.4 [0.0-98.3]	0.006
Red cell distribution width (%) ‡	14.8 [12.6-24.7]	14.9 [12.3-29.0]	0.355
Neutrophil/ lymphocyte ratio‡	19.6 [3.2-146.5]	32.1 [1.0-235.0]	<0.001
C-reactive protein&&/ albumin ratio‡	38.5 [6.0-85.7]	40.0 [3.0-88.0]	0.126
Creatinine (mg/dl)‡	1.0 [0.5-6.1]	1.1 [0.4-12.0]	0.011
Lactate dehydrogenase (U/L)‡	445.5 [103.0-2142.0]	542.0 [156.0-2751.0]	<0.001

‡: Median [min-max], *: Mann-Whitney U test, &: ACCESS immunoassay systems, method comparison (0.07-95.412 ng/ml), &&: Beckman Coulter Unicell DXI, high sensitive (0.2-480 mg/L)

Table 1. Demographic and clinical characteristics of the groups

	Overall (n=452)	Patient groups		p
		Survived (n=124)	Non-survived (n=328)	
Age (year)†,‡	71.3±13.6	68.7±14.0	72.3±13.3	0.010*
	72.0 [24.0-98.0]	69.0 [37.0-91.0]	73.5 [24.0-98.0]	
Sex§				
Female	204 (45.1)	56 (45.2)	148 (45.1)	0.999*
Male	248 (54.9)	68 (54.8)	180 (54.9)	
Comorbidities§				
Hypertension	157 (34.7)	46 (37.1)	111 (33.8)	0.591*
Neurological disorders	121 (26.8)	21 (16.9)	100 (30.5)	0.005*
Diabetes mellitus	89 (19.7)	28 (22.6)	61 (18.6)	0.414*
Coronary artery disease	91 (20.1)	26 (21.0)	65 (19.8)	0.888*
Chronic obstructive pulmonary disease	64 (14.2)	21 (16.9)	43 (13.1)	0.374*
Chronic renal failure	51 (11.3)	12 (9.7)	39 (11.9)	0.619*
Cancer	15 (3.3)	3 (2.4)	12 (3.7)	0.769*
APACHE II score ‡	21.0 [6.0-37.0]	19.0 [6.0-37.0]	22.0 [7.0-37.0]	<0.001**
Length of stay (day) ‡	9.00 [1.00-81.00]	8.0 [2.0-46.0]	10.0 [1.0-81.0]	0.307**

†: mean±standard deviation, ‡: median [min-max], §: n (%), *: Pearson x^2, Fisher's Exact test , **: Mann-Whitney U test

The non-surviving patients had higher leukocyte counts and PCT, NLR, creatinine, and LDH levels than the survivors. (Table 2).The median NLR was 32.1 and 19.6 in the non-surviving and surviving groups, respectively, and was statistically significant (p<0.001) (Figure 1).

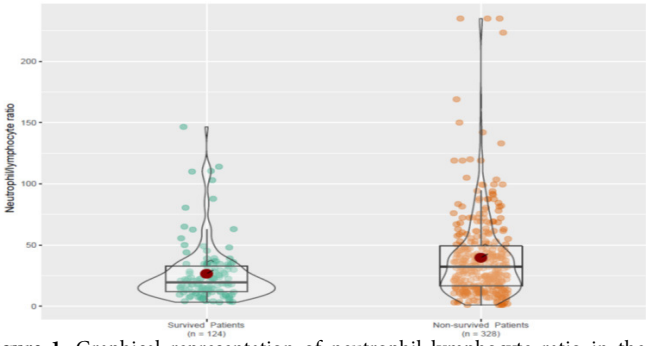

Figure 1. Graphical representation of neutrophil lymphocyte ratio in the survived and non-survived patients

In the study group, ROC curve analysis revealed significant laboratory parameter values and APACHE II scores (Table 3). The AUCs were 0.624 (95% CI: 0.577–0.669, p<0.001) for lymphocyte count, 0.618 (95% CI: 0.572–0.663, p<0.001) for APACHE II score, 0.617 (95% CI: 0.570–0.662, p<0.001) for LDH, 0.584 (95% CI: 0.537–0.630, p=0.005) for PCT, 0.572 (95% CI: 0.525–0.618, p=0.017) for leukocyte count, and 0.560 (95% CI: 0.513–0.607, p=0.037) for platelet count. The best cut-off point for lymphocyte count was ≤0.6 for predicting the mortality with a sensitivity and specificity of 78.05% and 41.94%, respectively (Figure 2).

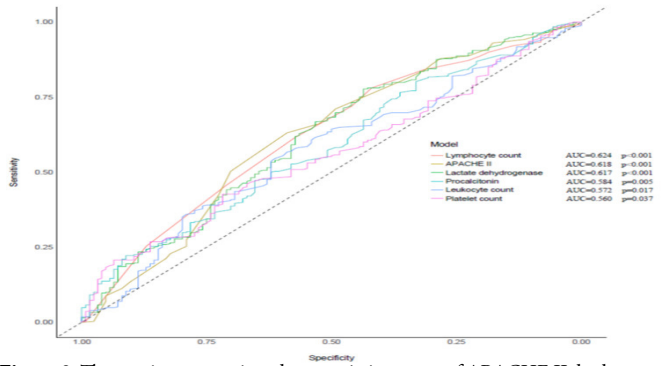

Figure 2. The receiver operating characteristic curves of APACHE II, leukocyte, lymphocyte, and platelet counts, procalcitonin, and lactate dehydrogenase
AUC: Area under the curve

Univariate logistic regression analysis revealed that age, APACHE II score, lymphocyte and platelet counts, PCT, NLR, creatinine, and LDH were significantly associated with mortality in patients with COVID-19 (Table 4). Multivariate logistic regression analysis revealed that age (OR=1.02, 95% CI: 1.000–1.0.4, p=0.018), APACHE II score (OR=1.01, 95% CI: 1.01–1.09, p=0.018), PCT (OR=1.05, 95% CI: 1.01–1.11, p=0.023), NLR (OR=1.02, 95% CI: 1.01–1.03, p=0.003), and LDH (OR=1.00, 95% CI: 1.00–1.00, p=0.0077) were the risk factors for prognosis in patients with COVID-19 (Figure 3).

Table 4. Logistic regression analysis of risk factors that impact on the development of mortality

	Univariate analysis	Multivariate analysis
	OR (95 CI%)	**OR** (95 CI%)
Age (year)	1.02 (1.00-1.03, p=0.013)	1.02 (1.00-1.04, p=0.018)
APACHE II score	1.07 (1.03-1.10, p=0.018)	1.05 (1.01-1.09, p=0.018)
Lymphocyte count	0.62 (0.43-0.89, p=0.009)	0.79 (0.52-1.24, p=0.295)
Platelet count	1.00 (1.00-1.00, p=0.022)	1.00 (1.00-1.00, p=0.287)
Procalcitonin	1.06 (1.02-1.12, p=0.014)	1.05 (1.01-1.11, p=0.023)
Neutrophil/ lymphocyte ratio	1.02 (1.01-1.03, p=0.003)	1.02 (1.01-1.03, p=0.003)
Creatinine (mg/dl)	1.20 (1.03-1.44, p=0.034)	1.07 (0.91-1.27, p=0.452)
Lactatedehydrogenase (U/L)	1.00 (1.00-1.00, p=0.003)	1.00 (1.00-1.00, p=0.007)

OR: Odds ratio, CI: confidence interval

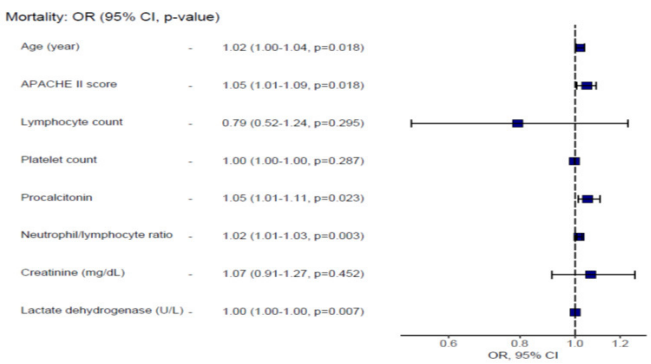

Figure 3. Multivariate logistic regression analysis of risk factors affecting mortality in COVID-19 patients
OR: Odds ratio, CI: confidence interval

Table 3. The area under curve analysis of the laboratory parameters and the APACHE II score in predicting the development of mortality

	AUC	Sensitivity	Specificity	Cut-off	95% CI	p
APACHE II	0.618	63.11	58.87	>20	0.572-0.663	<0.001
Leukocyte count	0.572	54.57	61.29	>11.9	0.525-0.618	0.017
Lymphocyte count	0.624	78.05	41.94	≤0.6	0.577-0.669	<0.001
Platelet count	0.560	42.68	71.77	≤194	0.513-0.607	0.037
Procalcitonin	0.584	22.26	91.13	>2.78	0.537-0.630	0.005
Red cell distribution width	0.528	47.87	66.13	>15	0.481-0.575	0.338
Neutrophil lymphocyte ratio	0.641	44.51	83.06	>36	0.595-0.686	0.641
CRP albumin ratio	0.547	29.88	79.03	>47	0.499-0.593	0.115
Creatinine	0.577	57.01	59.68	>1.01	0.530-0.623	0.577
Lactate dehydrogenase	0.617	77.74	43.55	>405	0.570-0.662	<0.001

AUC: Area under the curve, CI: confidence interval, CRP: C-reactive protein

DISCUSSION

Identifying high-risk patients with serious life-threatening diseases is important for predicting a poor clinical course, which contributes to the clinician's management of cases and hospital costs. In this study, the relationship between the demographic data recorded in the ICU of patients with COVID-19 and mortality was investigated. The power of inflammatory markers such as RDW, NLR, CRP/Alb, and PCT, measured as a result of COVID-19 infection, in predicting mortality was defined.

Although ICU mortality rates vary between 17% and 66.5% in patients with COVID-19,[4,5] different rates may be observed. Many studies have identified advanced age and high APACHE II scores as risk factors for mortality.[6,7] According to a study, men have a higher mortality risk than women.[8] The most common comorbidities upon ICU admission are HT, diabetes mellitus (DM), chronic obstructive pulmonary disease, heart disease, and chronic kidney disease (CKD), and their relationships with mortality have been shown.[1,3]

In our study, the 72.6% of our patients did not survive, and sex did not affect mortality. The increase in mortality with age observed in our study is consistent with that reported in the literature. The common comorbidities in patients admitted to the ICU because of COVID-19 were HT, neurological disorders, DM, and coronary artery disease. Furthermore, we found that neurological disorders, such as cerebrovascular and Alzheimer's diseases, were associated with mortality, and contrary to most of the literature, no relationship was observed between other comorbidities and mortality.

Considering laboratory parameters, previous studies have shown that increased D-dimer, CRP, urea, creatinine, RDW, LDH, and leukocyte count, as well as decreased albumin, lymphocyte counts, platelet counts, and arterial pH were detected in patients with COVID-19 and exitus patients.[1,3,7] Lee et al.[9] found a significant correlation between the depth of lymphopenia and mortality in a study conducted across the country and investigated the power of lymphopenia in predicting mortality. Similarly, Toori et al.[10] indicated a relationship between disease mortality, severity, and lymphopenia in their study.

In our study, we found that low lymphocyte and platelet counts and increased LDH, leukocyte, and creatinine levels were associated with mortality in terms of laboratory parameters.

Feng et al.[11] reported that high PCT levels were associated with both ICU demand and mortality in patients admitted to the ICU. Jackson et al.,[12] in their study investigating the relationship between PCT and the clinical course, found that high PCT levels indicate the severity of the disease; however, there was no relationship between hospital mortality and LoS in the hospital or ICU. In a multicenter study, Zattera et al.[13] reported that high PCT levels were not associated with mortality and that acute immunosuppression decreased PCT levels. In our study, a correlation was observed between increased PCT levels and increased mortality.

Many studies have investigated the relationship between the NLR and disease severity and mortality in different disease groups. In their study of patients with COVID-19, Imran et al.[14] found a relationship between the severity of COVID-19 pneumonia and NLR. King et al.[15] reported that a high NLR is associated with mortality and morbidity and is a guide for clinical follow-up and treatment. Moradi et al.[16] found a relationship between NLR and 30-day mortality. Yildiz et al.[17] found that an NLR value of 5.94 at admission to the hospital was associated with increased hospital mortality. In our study, a relationship was observed between increased NLR and mortality.

When we examined the roles of CRP/Alb and RDW in COVID-19, Lorente et al.[7] found a relationship between high RDW and 30-day mortality. Wang et al.[18] found that an increase in RDW levels showed the severity of the disease; however, they could not determine its effect on predicting hospital stay and mortality. Kalabin et al.[19] found that CRP/Alb was effective in determining the severity of COVID-19; however, they could not detect its effect on mortality. El-Shabrawy et al.[20] reported that CRP/Alb is a parameter that indicates disease severity and predicts mortality in patients with COVID-19. In our study, when patients who did not survive and those who survived were compared, both RDW and CRP/Alb were high. However, this difference was not statistically significant, and we could not detect the effects of either parameter on mortality recognition. We believe that the interleukin 6 blocker and high-dose steroids used in the treatment of COVID-19 may have affected the levels of some biomarkers and affected the results. Previous studies have shown that CRP can be affected by the attributed treatment leading to the difference in results between the literature and our study.[21]

In their study investigating the factors affecting mortality in patients with COVID-19, Vicka et al.[22] reported that APACHE II is a good scoring system. In a multicenter study, Ferrando et al.[23] found that the APACHE II score calculated upon admission was effective in predicting mortality. In our study, we found that the APACHE II score was effective in predicting mortality, which is consistent with the literature.

Limitations

Our study have some limitations, limitations of our study, the first is that it was retrospective in nature. Second, during the COVID-19 pandemic, it was difficult to reach the ICUs on busy days. During these periods, some treatments, such as tocilizumab and pulse steroids, were administered to patients in service patient rooms, and these treatments may have affected the levels of some laboratory parameters. At the same time, treatment modalities changed at the beginning and towards the end of the pandemic. This is also the case for oxygen support therapy, which may not have been standardized. In our study, we could not perform subgroup analyses of the patients who received these treatments. Finally, we could not determine secondary infections or the effects of these infections.

CONCLUSION

COVID-19 is a complex disease that can be diagnosed based on clinical presentation and laboratory parameters. The absence of specific and effective antiviral treatments can

lead to complications and superinfections. As in all patients followed up in the ICUs, both laboratory parameters and inflammatory biomarkers can help in the diagnosis, follow-up, and prognosis of COVID-19. Immunomodulators used in the treatment of COVID-19 can affect biomarker levels. This situation presents itself with different and even contradictory results in the literature. We believe that our study will contribute to the literature by predicting how similar situations can help clinicians treat COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee (Date: 22.06.2021, Decision No: 2021/161).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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